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Evaluation of the relationship between amitriptyline dose ingested and ADORA criteria in amitriptyline intoxication: A retrospective observational study

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Abstract

Aim: Amitriptyline exerts its effects on the central nervous system by inhibiting the reuptake of norepinephrine, dopamine, and serotonin. Amitriptyline's toxic effects occur 30 min after the ingestion of an excessive dose and peak within 2-6 h. While amitriptyline has a primarily anticholinergic effect at low doses, at high doses, it produces a potent depressive effect on the central nervous system, accompanied by cardiotoxicity, seizures, and hypotensive symptoms. The Antidepressant Overdose Risk Assessment (ADORA) criteria are used to evaluate clinical symptoms. In this study, we investigated the relationship between certain clinical and demographic parameters and the ADORA criteria in patients presenting to the emergency department with tricyclic antidepressant agent poisoning.

Material and Methods: The study included 18 patients admitted to the hospital between January 2016 and December 2019 following attempted suicide by amitriptyline overdose. Clinical and demographic data, ADORA risk classification, and ingested doses were recorded on a case-by-case basis. The relationship between ADORA risk classification, ingested dose, and other clinical parameters was analyzed.

Results: Of the patients included in the study, two were male (10.5%) and 16 were female (84.2%). The minimum ingested dose was 100 mg, maximum 525 mg, and median 300 mg. According to the ADORA criteria, 12 cases (66.7%) were classified as low-risk and six cases (33.3%) as high-risk. All the high-risk patients were hospitalized and treated ($p<0.0001$). The relationship between the amitriptyline dose ingested and ADORA classification was statistically significant ($p=0.02$). The sensitivity and specificity of this classification system for amitriptyline dose ingested were 100% and 60%, respectively, at a cut-off value of 285 mg and 60% and 100%, respectively, at a cut-off value of 350 mg.

Discussion: The ADORA risk classification system positively correlated with the hospitalization rate. Patients having ingested ≥350 mg of amitriptyline were classified as high-risk by the ADORA system with high specificity.

Keywords

Amitriptyline, Tricyclic Antidepressants, Antidepressants, Adrenergic Uptake Inhibitors, Prognosis

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Introduction

Amitriptyline (AMT) is a tricyclic antidepressant agent (TCA). Compounds containing AMT, imipramine, and other V-dimethyl derivatives came into use as antidepressants in the 1960s [1]. These agents act by inhibiting the reuptake of norepinephrine, dopamine, and serotonin from synapses in the central nervous system. Tricyclics are well absorbed from the gastrointestinal tract, transported through binding to plasma proteins, and eliminated by the hepatic metabolism [1].

Toxic effects start within 30 min following the excessive intake of TCA and peak in 2-6 h. Anticholinergic effects are dominant at low doses, while high doses of TCA produce significant depression in the central nervous system, accompanied by cardiotoxicity, seizures, and hypotensive symptoms [2]. Cardiotoxicities are associated with ventricular tachyarrhythmias, atrioventricular block, delays, bradycardia, and decreased cardiac output. Widening of the QRS complex is associated with increased cardiac arrhythmias and seizures [3]. The Antidepressant Overdose Risk Assessment (ADORA) criteria are used to evaluate clinical findings [4]. These criteria include QRS prolongation, arrhythmias, mental status changes, seizures, respiratory depression, and hypotension. Patients who do not meet any of these criteria at the time of admission to the emergency department (ED) within the first 6 h following TCA intake or those for whom the time of drug intake is not precisely known are classified as low-risk, while those meeting at least one of these criteria are classified as high-risk [4]. The current study aimed to determine the relationship between the clinical and demographic characteristics of patients who presented to the ED due to AMT intoxication and evaluate the relationship between the AMT dose ingested and the ADORA criteria.

Material and Methods

Study design

This retrospective descriptive study was conducted at University of Health Sciences Ümraniye Training and Research Hospital, a 682-bed tertiary academic education hospital with an annual ED census of 356,000 during the study period. We retrospectively collected the data of patients who presented to our ED with a history of AMT ingestion for suicidal purposes between January 1, 2016 and January 1, 2020. The flowchart of the study including the inclusion and exclusion criteria is shown in Figure 1.

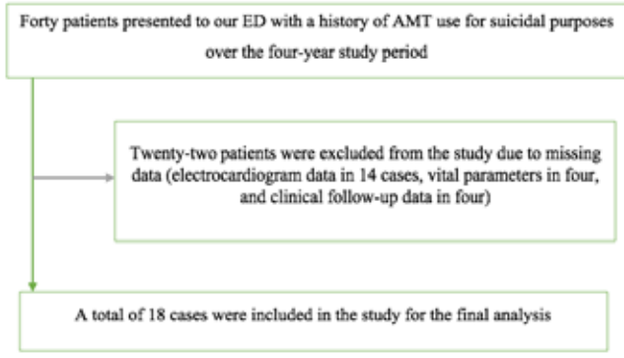

Figure 1. Flowchart of the study

Data collection

The clinical data of the patients, such as age, gender, pregnancy and lactation status, comorbidities, multiple drug use for suicidal purposes, initial ECG abnormalities, emergency service outcome, length of stay in the ED, treatment methods applied, necessity of inotrope use, mechanical ventilation requirement, and number of suicide attempts were recorded. The time from drug intake to admission to ED, dose of AMT taken, vital parameters, and Glasgow Coma Scale scores were documented. Vital parameters recorded were systolic and diastolic blood pressure, peripheral oxygen saturation, and pulse rate. From the laboratory parameters, the lactate level was noted. The ADORA criteria were evaluated by the researchers for each patient and their scores were calculated.

Statistical analysis

Categorical data were expressed as numbers and percentages and numerical data were expressed as minimum, maximum, and median values. IBM SPSS Statistics 27.0 for Mac (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The Mann-Whitney U test was used to compare ADORA scores with numerical data and Fisher's exact test was used to compare them with categorical data. In addition, receiver operating characteristic (ROC) curve analysis was performed between the drug dose used and the presence of ADORA criteria, and the cut-off value of this classification system was calculated. Results with a p-value below 0.05 were considered statistically significant.

Ethics

Ethical approval for the study was obtained from the Clinic Research Ethics Committee of University of Health Sciences Ümraniye Training and Research Hospital (approval number: 188; date: 06.17.2021). We retrospectively reviewed secondary data recorded from the computer-based system of the hospital. Informed consent was waived due to the documented clinical data not including any personal identifiable information.

Results

Of the total 18 cases included in the study (Figure 1), two patients (10.5%) were male and 16 (88.8%) were female. There were no pregnant women in our study population, and there was one lactating woman. According to the evaluation of the disease history and comorbidities of the patients, schizophrenia was present in one patient (5.5%), major depression in two

Table 1. Clinical characteristics of the patients

	Mean	Median	Min-max	IQR
Systolic blood pressure (mmHg)	128.9	126	108-170	15
Diastolic blood pressure (mmHg)	76	80	43-95	20
Pulse rate (/min)	86	80	46-160	17
Peripheral oxygen saturation	97	98	89-100	2
Glasgow Coma Scale score	14	14	5-15	0
Dose of amitriptyline taken (mg)	242.7	225	100-1000	200
Lactate level at admission (mmol/L)	1.28	1	0.01-6.4	1.23
Time from drug intake to ED admission (hours)	3.5	2	1-13	4
Length of ED stay (hours)	10.5	9	2-24	11

ED: Emergency department, IQR: interquartile range.

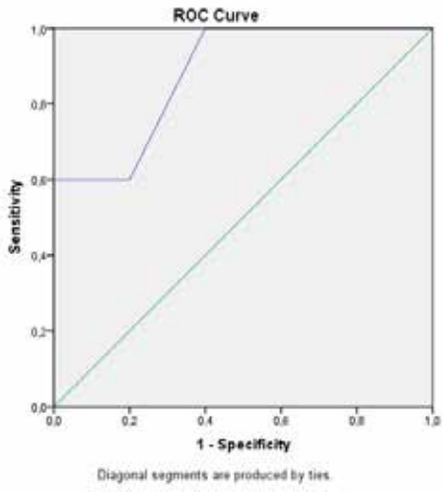

Figure 2. Receiver operating characteristic (ROC) curve analysis of the relationship between the ADORA classification and ingested amitriptyline dose

patients (11.1%), diabetes in one patient (5.5%), and migraine in one patient (5.5%). Half of the patients had taken multiple drugs. The minimum age was 22 years, maximum 52 years, and median 32 years. The clinical characteristics of the patients are shown in Table 1.

Detoxification by gastric lavage and repeated administration of activated charcoal were performed for 16 (88.8%) patients. Three of the patients (33.3%) were treated with lipid emulsion. None of the patients required inotropes in the ED. Two patients (11.1%) were mechanically ventilated. When initial ECG abnormalities were evaluated, sinus tachycardia was observed in three (16.6%) patients and QT prolongation in one (5.5%) patient.

According to the ADORA criteria, 12 cases (66.7%) were classified as low-risk and six (33.3%) as high-risk. There was no statistically significant correlation between ADORA and age, gender, systolic and diastolic blood pressure, pulse rate, peripheral oxygen saturation, multiple drug intake, ECG findings, lactate level at admission, treatment methods applied in the ED, mechanical ventilation requirement, time from drug intake to admission to ED, or length of ED stay ($p>0.05$).

Three-quarters of the low-risk patients were discharged, while the remaining one-quarter refused treatment and left the hospital. All high-risk patients were treated as inpatients ($p<0.0001$). The relationship between the AMT dose ingested and ADORA classification was also statistically significant ($p=0.02$). The ADORA criteria had sensitivity and specificity of 100% and 60%, respectively, at the cut-off value of 285 mg and 60% and 100%, respectively, at the cut-off value of 350 mg (Figure 2).

Discussion

In this study, the relationship between AMT level and ADORA criteria was investigated in patients with AMT poisoning admitted to our clinic. The results revealed that the AMT level was correlated with the ADORA criteria.

The ADORA criteria are used to evaluate the clinical findings of patients with antidepressant intoxication [5-8]. These criteria can distinguish serious toxicities in cases of antidepressant intoxication, allowing for daily follow-up and treatment plans to be carried out systematically. In addition, this classification can provide information on the differentiation of severe poisoning findings and possible clinical outcomes [7]. In a retrospective study conducted with 110 patients, Güllüoğlu et al. reported a correlation between the ADORA criteria and the dose of ingested AMT [8]. They showed a high level of correlation between AMT ingestion of greater than 500 mg and the ADORA criteria. In contrast, in our study with a similar methodology, we used the cut-off values of 285 mg and 350 mg for AMT and determined the sensitivity as 100% and 60%, respectively, and specificity as 60% and 100%, respectively. Although we evaluated a smaller population, our findings being in agreement with those of Güllüoğlu et al. support the clinical validity of our data. Both studies can be considered clinically important since the serum AMT level mostly cannot be tested in emergency services in Turkey, as is the case in many other parts of the world, or the patient cannot or does not provide medical history. According to the results of these two similar studies, the ADORA criteria can be used in clinical decision-making in cases where clinicians need to make treatment decisions according to the patient's clinical state.

Intravenous lipid emulsion therapy was first used in 2006 by Rossenbalt et al. in the treatment of asystole due to bupivacaine, a local anesthetic [9]. Lipid emulsion therapy is defined as the intravenous use of lipid emulsions to reduce the bioavailability and toxicity of circulating lipophilic toxic substances [10]. This method, which is generally preferred for the treatment of systemic toxicity, aims to rapidly lower the content of lipid-soluble compounds in the blood through an initial high-dose bolus administration followed by a constant-rate infusion. In the current literature, it is suggested that lipid emulsion therapy can be used in cases of AMT intoxication [10, 11]. Bora et al. investigated the effectiveness of MgSO4, metoprolol, and lipid emulsion treatments in preventing the cardiac toxicity of AMT overdose in an experimental study and reported that all three treatment options were effective in rats with elongated QTc associated with AMT overdose [12]. In an experimental study on guinea pigs, Tsujikawa et al. suggested that lipid emulsion was a superior first-line therapy method for TCA-induced cardiotoxicity compared to alkalinization therapy [13]. There may be several logical explanations for this positive effect of lipid therapy. One possibility is that emulsified oil droplets form a lipid compartment in the plasma and AMT is drawn into this compartment, thus moving away from areas with high blood flow, such as the heart, kidneys, and brain, where lipophilic substances are present in high concentrations [10-13]. Another mechanism could be the direct inotropic effect of lipids on cardiac work [10-13]. In our cohort, three patients received lipid emulsion therapy and all achieved clinical improvement.

Suicidal drug use is a more common behavior among women than men worldwide [12,13]. In our sample, about four-fifths of the patients were female. Among the reasons for this are gender-related characteristics, cultural and social pressure, and not being able to meet societal expectations of the female gender [14-16].

A quarter of our low-risk patient population withdrew from treatment and did not fully attend the recommended close

follow-up. In clinical practice, the legal guardians of suicidal patients who have withdrawn from treatment are also asked to confirm this decision; however, certain legal problems may still arise for clinicians [17]. Withdrawal from treatment is an important problem in cases of intoxication [18]. The treatment of especially high-risk patients should be enforced with legal arrangements. It is also important to improve health literacy to ensure compliance with current scientific treatment by patients and their relatives [19].

Limitations

The main limitation of this study is its retrospective design. Less biased results can be obtained with prospective studies. Due to the retrospective design, we were not able to access the data of 22 patients, which limited our cohort. Secondly, our study was conducted in a single center with an observational design; therefore, the results cannot be generalized to other healthcare institutions. Thirdly, in this study, we evaluated the intoxication and dose of a specific drug, which further limited the number of cases. This is a general problem of studies conducted in the field of toxicology, especially for specific drugs. A plausible explanation for this may be that clinicians prefer selective serotonin reuptake inhibitor group antidepressants over AMT because selective serotonin reuptake inhibitors have a wide margin of safety and less danger of producing toxic effects with a high therapeutic index. Finally, the generalizability of our study should be increased with larger populations and multicenter studies.

Conclusion

The ADORA risk classification system positively correlated with the hospitalization rate. Patients having ingested ≥350 mg of AMT were classified as high-risk by the ADORA system with high specificity. However, the generalizability of this finding should be increased by further studies with larger populations and multicenter designs.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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